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Mental health conditions and bleeding events in patients with incident atrial fibrillation: A Finnish nationwide cohort study

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ABSTRACT

Objective: We assessed the hypothesis that mental health conditions (MHCs) are associated with higher risk of bleeding in patients with atrial fibrillation (AF).
Methods: The registry-based FinACAF study covers all patients with AF diagnosed during 2007–2018 in Finland. MHCs of interest were depression, bipolar disorder, anxiety disorder, schizophrenia, and any MHC. The outcomes were first-ever gastrointestinal, intracranial, and any bleeding event.
Results: We identified 205,019 patients (50.9% female; mean age 72.3 [standard deviation 13.4] years) with incident AF without prior bleeding, and the prevalence of any MHC was 6.1%. Any MHC, depression, and anxiety disorder were associated with the risk of any bleeding (adjusted hazard ratios (HRs) 1.19 [1.12–1.27], 1.21 [1.13–1.30], and 1.21 [1.08–1.35], respectively). Additionally, any MHC and depression were associated with the risk of gastrointestinal and intracranial bleeding and anxiety disorder with gastrointestinal bleeding. Bipolar disorder and schizophrenia were not associated with risk of bleeding. Use of oral anticoagulants was associated with the risk of any bleeding (adjusted HR 1.24 [95% CI 1.21–1.28)]), and this association was similar in patients with and without MHCs. Serotonin reuptake inhibitors were not associated with bleeding risk.
Conclusions: MHCs are associated with a higher risk of bleeding in patients with AF.

1. Introduction

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia with a lifetime risk of 1 in 3 individuals, is associated with considerably increased risk of ischemic stroke and mortality [1,2]. While oral anticoagulant (OAC) therapy effectively mitigates both the risk of stroke and death in high-risk patients with AF, it also predisposes patients to bleeding events [1,3]. Therefore, evaluation of patient's bleeding risk and management of modifiable bleeding risk factors is essential for optimal stroke prevention therapy, and several risk stratification scores have been generated to guide clinical decision making [2].

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Mental health conditions (MHCs) are exceedingly prevalent and associated with poor outcomes [4–6]. The authors have previously reported that MHCs are associated with lower use of OAC therapy and higher mortality in patients with AF [7,8]. Bleeding risk factors prevail in patients with MHCs, and additionally, several studies have linked MHCs and psychotropic medications with platelet dysfunction [9–11]. Indeed, patients with MHCs have been reported to experience bleeding events at a higher rate than patients without MHCs, regardless of the presence of AF [12–14]. However, data on the risk of bleeding in patients with AF and MHCs is limited. We conducted a nationwide retrospective cohort study to assess the hypothesis that MHCs are associated with higher risk of bleeding in patients with AF.

2. Methods

2.1. Study population

The Finnish AntiCoagulation in Atrial Fibrillation (FinACAF) Study (ClinicalTrials Identifier: NCT04645537; ENCePP Identifier: EUPAS29845) is a nationwide retrospective cohort study including all patients with an AF diagnosis in Finland during 2004–2018 [15]. Patients were identified from all available national health care registers (hospitalizations and outpatient specialist visits: HILMO; primary health care: AvoHILMO; and National Reimbursement Register upheld by Social Insurance Institute: KELA). The inclusion criterion for the cohort was an International Classification of Diseases, Tenth Revision (ICD-10) diagnosis code I48 (including atrial fibrillation and atrial flutter, together referred as AF) recorded between 2004 and 2018 and cohort entry occurred on the date of the first recorded AF diagnosis. The exclusion criteria were permanent migration abroad before December 31st 2018 and age < 18 years at AF diagnosis. The current substudy was conducted within a cohort of patients with incident AF between 2007 and 2018, established in previous studies of the FinACAF cohort [16–18]. Patients with bleeding events before cohort entry were excluded. Information on prior bleeding events and baseline characteristics were gathered from 2004 onwards until the first AF diagnosis. Follow-up continued until the first bleeding event of interest, death or 31st December 2018. The patient selection process is summarized in Supplementary Fig. 1.

2.2. Mental health conditions

MHCs of interest were depression, bipolar disorder, anxiety disorder, schizophrenia. These conditions were chosen due to their high prevalence in the aging population of patients with AF [6]. Patients were classified into diagnostic groups if they were recorded with the ICD-10 diagnosis code or International Classification of Primary Care, Second Edition (ICPC-2) entry of the condition before the index date as follows: depression (ICD-10: F32, F33, F34.1; ICPC-2: P76), anxiety disorder (ICD-10: F40-F42, F43.1; ICPC-2: P74), bipolar disorder (ICD-10: F31; ICPC-2: P73), schizophrenia (ICD-10: F20; ICPC-2: P72). Patients with more than one of these conditions were classified into each diagnostic category separately. Patients were classified to have any MHC if they had any of these four MHCs. Patients without the aforementioned MHCs and without prescription of an antidepressant, antipsychotic, or mood stabilizing medication within the year before the index date were classified to have no MHC (Anatomical Therapeutic Chemical codes: N05A, N05BE01, N06A). Additionally, to account for possible information bias due to inaccurate recording of MHC diagnose codes, sensitivity analyses were performed on patients with any diagnosed MHC or use of the abovementioned psychotropic medications.

2.3. Outcomes

The outcomes of interest were the first-ever any bleeding, gastrointestinal (GI) bleeding and intracranial (IC) bleeding events. The outcome was considered to occur on the first date of a recorded bleeding diagnosis. The diagnosis codes and dates were searched from the HILMO hospital care register. The ICD-10 codes used to define outcome events are summarized in Supplementary Table 1.

2.4. Study ethics

The study protocol was approved by the Ethics Committee of the Medical Faculty of Helsinki University, Helsinki, Finland (nr. 15/2017) and granted research permission from the Helsinki University Hospital (HUS/46/2018). Respective permissions were obtained from the Finnish register holders (KELA 138/522/2018; THL 2101/5.05.00/2018; Population Register Centre VRK/1291/2019–3; Statistics Finland TK-53-1713-18 / u1281; and Tax Register VH/874/07.01.03/2019). The patients' identification numbers were pseudonymized, and the research group received individualized, but unidentifiable data. Informed consent was waived due to the retrospective registry nature of the study. The study conforms to the Declaration of Helsinki as revised in 2013.

2.5. Statistical analysis

The chi-square test was used to compare differences between proportions, and the independent samples *t*-test to analyze continuous variables. Cox proportional hazards regression was used to estimate the unadjusted and adjusted bleeding hazard ratios. The outcome was the first-ever bleeding type of interest, and patients were censored at death or at the end of observation period on 31st December 2018. The adjusted analyses included the following variables: age, gender, calendar year of AF diagnosis, dementia, cancer, alcohol use disorder, prior stroke, abnormal liver function, abnormal kidney function, diabetes, hypertension, any vascular disease, heart failure, income quartiles and use of serotonin reuptake inhibitors (SRI; covering selective serotonin reuptake inhibitors and serotonin-noradrenalin reuptake inhibitors) and OACs (warfarin, dabigatran, apixaban, rivaroxaban or edoxaban). OAC and SRI exposures were treated as time-dependent variables, and exposure was considered to start from the first drug purchase date and continue until 135 days after the last drug purchase during follow-up. The 135-day interval was chosen since in Finland it is possible to purchase drugs with reimbursement for a maximum of 90 days and an additional 45-day grace period was allowed to cover possible stockpiling and differences in warfarin dosing. An interaction term between MHC categories and follow-up time, along with the inspection of log-negative log survival curves, indicated that the proportional hazards assumption was met. No significant multicollinearity between the independent variables was observed. Additionally, to determine whether the association between OAC exposure and bleedings differs between patients with and without MHCs, an interaction term between the time-dependent OAC exposure variable and any MHC was fitted in the Cox regression model. Furthermore, an e-value was calculated to measure the strength of association that an unmeasured confounder would need to have with both any MHC and any bleeding to fully explain away any observed association. The definitions of the comorbidities are displayed in Supplementary Table 1. Statistical analyses were performed with the IBM SPSS Statistics software (version 27.0, SPSS, Inc., Armonk, NY) and R (version 4.0.5, https://www.R-project.org).

3. Results

We identified 205,019 patients (50.9% female; mean age 72.3 (SD 13.4) years) with incident AF without prior bleedings. The prevalence of any MHC at cohort entry was 6.1%. Mean follow-up time in the any bleeding analyses was 4.0 (SD 3.2) years, and the incidence rate of first-ever any bleeding was 3.06 (95% CI 3.03–3.10) per 100 patient-years. Patients with MHCs were more often female, had lower income and higher prevalence of cardiovascular comorbidities than patients with no history of MHC (Table 1). Overall, OAC therapy was initiated in 147,098

Table 1
Descriptive characteristics of the study cohort according to the presence of MHCs.

	No MHC	Any MHC	Depression	Bipolar disorder	Anxiety disorder	Schizophrenia	Any MHC or psychotropic drug use
	n = 165,514	n = 12,413	n = 8928	n = 924	n = 3617	n = 1323	n = 39,505
Demographics							
Mean age, years	72.3 (13.1)	69.0 (14.6)*	69.4 (14.5)*	64.0 (13.0)*	65.8 (16.3)*	69.4 (11.7)*	72.5 (14.3)*
Female sex	80,201 (48.5)	7462 (60.1)*	5471 (61.3)*	454 (49.1)	2246 (62.1)*	717 (54.2)*	24,117 (61.2)*
Income quartiles		*	*	*	*	*	*
1st	39,880 (24.1)	5084 (41.0)	3338 (37.4)	447 (48.4)	1515 (41.9)	971 (73.4)	13,496 (34.2)
2nd	39,604 (23.9)	3132 (25.2)	2370 (26.5)	190 (20.6)	920 (25.4)	188 (14.2)	9707 (24.6)
3rd	42,616 (25.7)	2353 (19.0)	1812 (20.3)	159 (17.2)	673 (18.6)	98 (7.4)	8692 (22.0)
4th	43,414 (26.2)	1844 (14.9)	1408 (15.8)	128 (13.9)	509 (14.1)	66 (5.0)	7610 (19.3)
Comorbidities							
Alcohol use disorder	3916 (2.4)	1794 (14.5)*	1388 (15.5)*	243 (26.3)*	574 (15.9)*	126 (9.5)*	3232 (8.2)*
Cancer	31,998 (19.3)	2244 (18.1)*	1707 (19.1)	121 (13.1)*	605 (16.7)*	189 (14.3)*	8056 (20.4)*
Dementia	5440 (3.3)	1103 (8.9)*	864 (9.7)*	49 (5.3)	212 (5.9)*	120 (9.1)*	4417 (11.2)*
Diabetes	33,431 (20.2)	3274 (26.4)*	2350 (26.3)*	294 (31.8)*	804 (22.2)*	475 (35.9)*	9450 (23.9)*
Dyslipidemia	76,898 (46.5)	6077 (49.0)*	4546 (50.9)*	457 (49.5)	1708 (47.2)	511 (38.6)*	19,350 (49.0)*
Heart failure	26,268 (15.9)	2240 (18.0)*	1562 (17.5)*	147 (15.9)	530 (14.7)*	387 (29.3)*	31,807 (19.5)*
Hypertension	119,337 (72.1)	9548 (76.9)*	6994 (78.3)*	694 (75.1)	2832 (78.3)*	878 (66.4)*	30,817 (78.0)*
Liver cirrhosis or failure	535 (0.3)	84 (0.7)*	67 (0.8)*	9 (1.0)	23 (0.6)*	6 (0.5)	206 (0.5)*
Renal failure or dialysis	5390 (3.3)	570 (4.6)*	418 (4.7)*	50 (5.4)*	168 (4.6)*	46 (3.5)	1697 (4.3)*
Prior stroke	15,187 (9.2)	1411 (11.4)*	1044 (11.7)*	109 (11.8)*	368 (10.2)	145 (11.0)	4517 (11.4)*
Any vascular disease	43,220 (26.1)	3385 (27.3)*	2549 (28.6)*	198 (21.4)*	895 (24.7)*	300 (22.7)*	11,522 (29.2)*
Risk scores							
CHA_2DS_2-VASc score	3.3 (1.9)	3.4 (1.9)*	3.5 (1.9)*	2.9 (1.9)*	3.2 (1.9)*	3.4 (1.8)*	3.4 (1.8)*
Modified HAS-BLED score(max 8)	2.3 (1.0)	2.5 (1.0)*	2.5 (1.0)*	2.5 (1.0)*	2.5 (1.0)*	2.2 (1.0)*	2.2 (1.0)*
Medications							
Antiplatelet/NSAIDs at baseline	49,256 (29.8)	4118 (33.2)*	3112 (34.9)*	330 (35.7)*	1271 (35.1)*	259 (19.6)*	13,664 (34.6)*
SRIs at baseline	0 (0)	4766 (38.4)*	3892 (43.6)*	297 (32.1)*	1480 (40.9)*	223 (17.6)*	14,299 (36.2)*
OAC during follow-up	121,230 (73.2)	8125 (65.5)*	5927 (66.4)*	604 (65.4)*	2286 (63.2)*	810 (61.2)*	25,868 (65.5)*

Values denote n (%) or mean (standard deviation). Abbreviations: CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes, history of stroke or TIA, vascular disease, age 65–74 years, sex category (female); MHC, mental health condition; modified HAS-BLED score, hypertension, abnormal renal or liver function, prior stroke, bleeding history, concomitant antiplatelet/NSAIDs use, age > 65 years, alcohol abuse (no labile INR, max score 8).* $p < 0.05$ when compared to patients without MHC.

patients (71.1%), in whom the initial anticoagulant was warfarin in 68.2% and direct oral anticoagulant in 31.8% of cases. Patients with MHCs initiated OAC therapy less often than patients without MHC (Table 1).

Overall, the crude incidence rates of all bleeding categories were higher in patients with any MHC or depression than in patients without MHC (Fig. 1, Table 2). Additionally, higher crude incidence of GI bleeding was observed in patients with anxiety disorder. In other MHC categories, no statistically significant differences in crude bleeding incidence were observed, when compared to patients without MHC (Table 2). In the sensitivity analyses, patients with any diagnosed MHC or use of psychotropic medications at cohort entry had a higher crude incidence rate of any bleeding than patients without MHC (Supplementary Table 2). The crude disparity between patients with and without MHCs in the rate of any bleeding was larger among patients under 65 years than among older patients (Supplementary Table 3). The e-value for the association between any MHC and any bleeding was 1.67.

After adjusting for confounding factors, any MHC and depression were associated with the hazard of any bleeding, as well as GI and IC bleedings. Additionally, anxiety disorder was associated with the hazard of any bleeding and GI bleeding. In other MHC and bleeding categories, the adjusted risk estimates were not statistically significant (Table 3). Exposure to OACs was associated with the hazard of any bleeding (adjusted HR 1.24 (95% CI 1.21–1.28)), and this association was similar in patients with and without MHCs (interaction term: OAC exposure x any MHC, adjusted HR 1.05 (95% CI 0.97–1.13), $p = 0.25$). No association was observed between the SRI exposure and any bleeding (adjusted HR 0.97 (95% CI 0.86–1.10)). When compared to patients without MHCs, the adjusted hazard of any bleeding in patients with any MHC was similar among men and women, as well as among patients under and over 65 years (Supplementary Table 3). In the sensitivity analyses, patients with any diagnosed MHC or use of psychotropic medications had a higher adjusted hazard of any bleeding (Supplementary Table 2).

4. Discussion

This nationwide cohort study in patients with incident AF and without prior bleedings demonstrated, that MHCs are associated with a higher risk of bleeding. Any MHC was associated with the hazard of any bleeding, as well as with the hazard of GI and IC bleeding, both before and after adjusting for confounding factors. Regarding the specific MHC categories, depression was associated with all bleeding categories and anxiety disorder with any bleeding and GI bleeding. On the other hand,

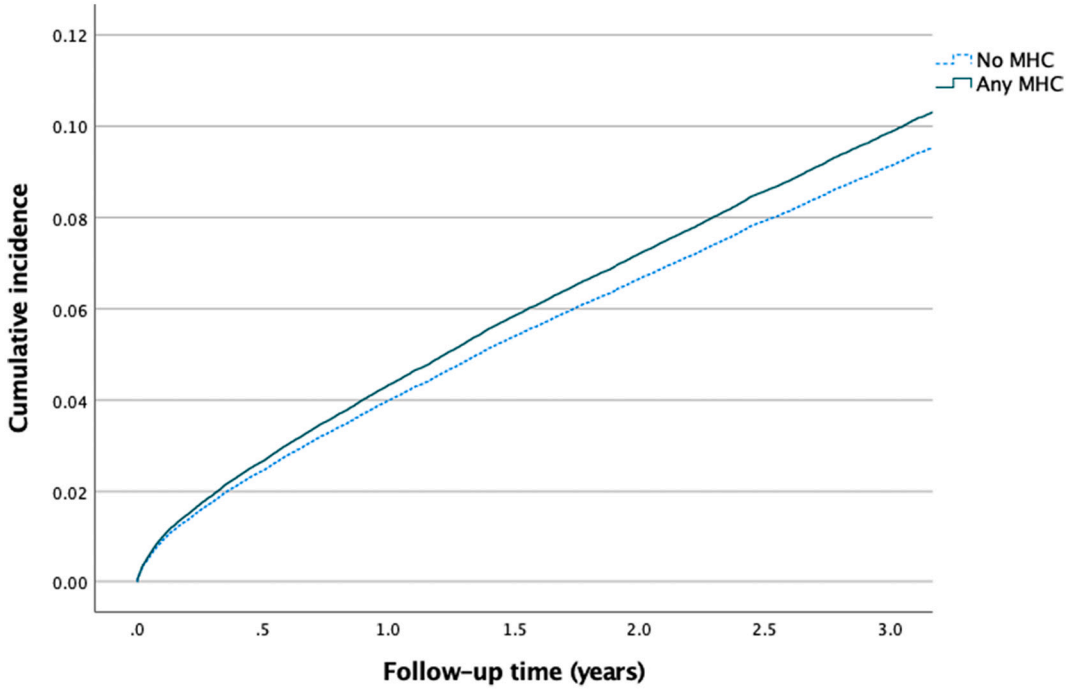

Fig. 1. Crude cumulative incidence curve of any bleeding according to the presence of any MHC.

Table 2
Crude incidence of bleeding according to the presence of MHCs.

	Any bleeding			GI bleeding			IC bleeding		
	Events, n (%)	P-years (100 years)	Incidence rate (per 100 p-years)	Events, n (%)	P-years (100 years)	Incidence rate (per 100 p-years)	Events, n (%)	P-years (100 years)	Incidence rate (per 100 p-years)
Clinical condition									
No MHC	20,037 (12.1)	6686.6	3.00 (2.96–3.04)	6743 (4.1)	7018.5	0.96 (0.94–0.98)	4784 (2.9)	7087.2	0.68 (0.66–0.70)
Any MHC	1328 (10.7)*	1472.5	3.35 (3.17–3.54)*	514 (4.1)	1549.8	1.19 (1.13–1.24)*	334 (2.7)	1570.9	0.79 (0.71–0.88)*
Depression	1000 (11.2)*	285.2	3.51 (3.30–3.73)*	392 (4.4)	298.4	1.31 (1.19–1.45)*	251 (2.8)	303.4	0.83 (0.73–0.94)*
Bipolar disorder	96 (10.4)	32.8	2.93 (2.40–3.58)	32 (3.5)	34.0	0.94 (0.67–1.33)	26 (2.8)	34.4	0.76 (0.51–1.11)
Anxiety disorder	351 (9.7)*	112.3	3.13 (2.81–3.47)	148 (4.1)	116.7	1.26 (1.08–1.49)*	80 (2.2)*	119.0	0.67 (0.54–0.84)
Schizophrenia	110 (8.3)*	39.2	2.81 (2.33–3.39)	42 (3.2)	40.3	1.04 (0.77–1.41)	32 (2.4)	40.9	0.78 (0.55–1.11)

Abbreviations: GI, gastrointestinal; IC, intracranial; MHC, mental health condition. 95% confidence intervals in parenthesis. * = $p < 0.05$ when compared with patients without MHC.

Table 3
Hazard ratios of bleeding according to the presence of MHCs.

	Any bleeding		GI bleeding		IC bleeding	
Clinical condition	Unadjusted HR	Adjusted HR	Unadjusted HR	Adjusted HR	Unadjusted HR	Adjusted HR
No MHC	(Reference)	(Reference)	(Reference)	(Reference)	(Reference)	(Reference)
Any MHC	1.09 (1.03–1.15)	1.19 (1.12–1.27)	1.25 (1.14–1.36)	1.19 (1.08–1.32)	1.17 (1.05–1.31)	1.19 (1.05–1.34)
Depression	1.14 (1.07–1.22)	1.21 (1.13–1.30)	1.32 (1.19–1.46)	1.22 (1.09–1.37)	1.22 (1.08–1.39)	1.18 (1.02–1.36)
Bipolar disorder	0.96 (0.79–1.18)	1.10 (0.90–1.35)	0.96 (0.78–1.36)	0.95 (0.67–1.35)	1.12 (0.76–1.64)	1.27 (0.86–1.88)
Anxiety disorder	1.01 (0.91–1.13)	1.21 (1.08–1.35)	1.26 (1.07–1.49)	1.31 (1.10–1.56)	0.99 (0.80–1.25)	1.11 (0.87–1.39)
Schizophrenia	0.91 (0.76–1.10)	0.99 (0.82–1.20)	1.03 (0.76–1.40)	0.97 (0.71–1.31)	1.15 (0.82–1.63)	1.22 (0.86–1.74)

Abbreviations: GI, gastrointestinal; HR, hazard ratio; IC, intracranial; MHC, mental health condition. 95% confidence intervals in parenthesis. HRs estimated by Cox regression and adjusted for: age, gender, cohort entry year, dementia, cancer, alcohol use disorder, prior stroke, abnormal liver function, abnormal kidney function, diabetes, hypertension, any vascular disease, heart failure and income quartiles and use of serotonin reuptake inhibitors and oral anticoagulants.

bipolar disorder and schizophrenia were not associated with higher bleeding risks. The association between MHCs and bleeding was similar among men and women, as well as among patients under and over 65 years.

Previous research on the association of MHCs and bleeding in patients with AF is limited and has provided inconsistent results. While the two most recent studies in this field, conducted in Denmark and in the United States, found no association between MHCs and bleeding events,

three older studies have reported of such an association [14,19–22]. Furthermore, our recently published meta-analysis pooling the results of these five observational studies reported a 17% higher bleeding risk in AF patients with MHCs [7]. However, all these previous original contributions may have been prone to major selection, confounding, and information biases owing to selected patient populations, insufficient controlling for confounding factors, and lack of primary care data. Patients treated solely in the primary care are typically older, with higher bleeding risks, and the exclusion of these patients may significantly hinder the generalizability of previous findings. Additionally, socioeconomic factors, known to associate with bleeding risks, have not been accounted for in the previous studies [23]. Furthermore, with the exception of the Danish work by Søgaard et al., all prior studies have included only patients already receiving warfarin therapy and thus deemed suitable recipients of OAC treatment [19]. Therefore, the current large nationwide study with comprehensive data on all patients with incident AF from all levels of care considerably expands our understanding on the associations between MHCs and bleeding risk.

The most evident, approximately 20% higher, hazards of all bleeding categories were observed in patients with any MHC and depression. Additionally, a trend towards increased bleeding risks was observed across the MHC and separate bleeding categories, although not all associations reached statistical significance, which may partly be related to the relatively small number of patients in the specific MHC groups. Nevertheless, no increased bleeding risks were observed in patients with bipolar disorder or schizophrenia, possibly signaling differences between MHCs in the underlying mechanisms predisposing to bleeding. Interestingly, the two most recent studies assessing stroke risk in patients with AF and MHCs reported that MHCs do not independently increase the risk of ischemic stroke [8,19]. In contrast, MHCs are associated with higher bleeding risks in our study, emphasizing the importance of appropriate bleeding risk assessment and management of modifiable bleeding risk factors in this considerably large and vulnerable patient group. Nevertheless, in our adjusted interaction analyses, the association between OAC use and bleeding was similar in patients with and without MHCs, indicating that notwithstanding the observed higher bleeding risks in patients with MHCs, OAC therapy *per se* does not entail more risks in patients with MHCs than among those without MHC. Hence, there seems to be no clinical grounds for the previously observed poorer OAC coverage among patients with MHCs [16,24]. Interestingly, contrary to previous findings, use of SRIs was not associated with bleeding risk in our analyses, possibly suggesting that the factors linking MHCs with bleeding risks may partly explain the bleeding risks associated with SRIs in previous observational studies [25].

The observed disparities in bleeding risks between patients with and without MHCs are likely multifactorial. The higher prevalence of bleeding risk factors and other comorbidities in patients with MHCs undoubtedly affect bleeding risks, but these factors, as well as age differences, were accounted for in our adjusted analyses. Hence, the bleeding risks associated with MHCs are not completely explained by the factors incorporated in the widely used bleeding risk stratification tools. Additionally, patients with MHCs have more often undiagnosed comorbidities, and their known comorbidities are frequently undertreated [26,27]. Moreover, poor treatment adherence often further decreases the benefits of initiated therapies in this patient group [27,28]. Likewise, MHCs have been associated with poorer anticoagulation control with warfarin, which may reflect in their higher bleeding risk [14]. Fragmented care due to the separation of psychiatric and somatic healthcare services as well as poorer self-care resources associated with MHCs may be underlying these shortfalls in treatment. On the other hand, the authors have previously reported that MHCs do not meaningfully affect adherence to DOAC therapy in patients with AF [29]. Furthermore, unhealthy life-style habits, such as tobacco use, are also common in patients with mental illnesses, and although our data covered diagnosed alcohol use disorders, patients with MHCs may have higher alcohol consumption below the threshold of clinical diagnosis [30,31].

The most important limitations of our study are the challenges inherent to retrospective cohort studies based on administrative data. Hence, our results reflect associations and not necessarily causation, and confounding and information biases owing to unmeasured or inappropriately recorded data may affect our results. Furthermore, due to the limitations of our data, we were unable to account for repeat bleeding episodes, and therefore focused our analyses on the rate of the first-ever bleeding event. Additionally, the exclusion of patients with prior bleedings or anemia due to bleeding may bias our findings. We lacked data on life-style related factors, except for diagnosed alcohol use disorders. Moreover, we did not consider use of nonsteroidal anti-inflammatory drugs and low-dose acetylsalicylic acid in the adjustments since they are frequently purchased over the counter without prescription in Finland. OAC and SRI exposures are based on pharmacy purchase dates, and both the claimed medication quantity and whether patients actually took these medications are unknown. Also, selection bias may be present in the results regarding the risks related to OAC use, since OACs have likely been initiated on a selected patient population. Notwithstanding these limitations, major strengths of our study are the large nationwide study sample and the comprehensive medical data from all levels of care. Additionally, the used validated national registries have relatively high diagnostic accuracy, especially regarding cardiovascular diseases [32].

The findings of this nationwide retrospective cohort study accentuate higher bleeding risks among patients with AF comorbid with MHCs, and highlight the importance of appropriate bleeding risk assessment as well as management of modifiable bleeding risk factors in this vulnerable patient group. Clinicians should be aware of the higher bleeding risks in patients with MHCs, and future research needs to explore effective interventions to improve their outcomes.

Author contributions

Dr. Teppo had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Teppo, Jaakkola, Putaala, Mustonen, Airaksinen, Lehto.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Teppo.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Teppo, Jaakkola.

Obtained funding: Lehto.

Administrative, technical, or material support: Jaakkola, Halminen.

Supervision: Jaakkola, Putaala, Mustonen, Airaksinen, Lehto.

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The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data availability statement

Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the Finnish national register holders (KELA, Finnish Institute for Health and Welfare, Population Register Center and Tax Register) through Findata (https://findata.fi/en/).

Declaration of Competing Interest

Konsta Teppo: none. Jussi Jaakkola: none. Fausto Biancari: none Olli Halminen: none. Jukka Putaala: Dr. Putaala reports personal fees from Boehringer-Ingelheim, personal fees and other from Bayer, grants and personal fees from BMS-Pfizer, personal fees from Portola, other from Amgen, personal fees from Herantis Pharma, personal fees from Terve Media, other from Vital Signum, personal fees from Abbott, outside the submitted work. Pirjo Mustonen: Consultant: Roche, BMS-Pfizer-alliance, Novartis Finland, Boehringer Ingelheim, MSD Finland. Miika Linna: Speaker: BMSPfizer-alliance, Bayer, Boehringer-Ingelheim. Juha Hartikainen: Research grants: The Finnish Foundation for Cardiovascular Research, EU Horizon 2020, EU FP7. Advisory Board Member: BMS-Pfizer-alliance, Novo Nordisk, Amgen. Speaker: Cardiome, Bayer. K.E. Juhani Airaksinen: Research grants: The Finnish Foundation for Cardiovascular Research; Speaker: Bayer, Pfizer and Boehringer-Ingelheim. Member in the advisory boards: Bayer, Pfizer and AstraZeneca. Mika Lehto: Consultant: BMS-Pfizer-alliance, Bayer, Boehringer-Ingelheim, and MSD; Speaker: BMS-Pfizer-alliance, Bayer, Boehringer Ingelheim, MSD, Terve Media and Orion Pharma. Research grants: Aarne Koskelo Foundation, The Finnish Foundation for Cardiovascular Research, and Helsinki and Uusimaa Hospital District research fund, Boehringer-Ingelheim.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.genhosppsych.2022.08.003.

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